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REVIEW

Clinical update

Role of neprilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials

Chirag Bavishi[1], Franz H. Messerli[2,3]*, Bernard Kadosh[1], Luis M. Ruilope[4], and Kazuomi Kario[5]

[1]Mount Sinai St Luke's & Roosevelt Hospitals, New York, NY, USA; [2]Division of Cardiology, Mount Sinai Medical Center, Icahn School of Medicine, 1 Gustave L. Levy Pl, New York, NY 10029, USA; [3]Department of Cardiology, Bern University Hospital, Bern, Switzerland; [4]Hospital 12 de Octubre, Madrid, Spain; and [5]Jichi Medical University School of Medicine, Tochigi, Japan

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Neprilysin is a neutral endopeptidase and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatatory, and anti-proliferative effects. In concert, these effects are prone to produce a powerful ventricular unloading and anti-hypertensive response. LCZ696 (Valsartan/sacubitril) is a first-in-class angiotensin II-receptor neprilysin inhibitor. LCZ696 is a novel drug not only for the treatment of heart failure but it is also likely to be a useful antihypertensive drug and may have a preferential effect on systolic pressure. This review discusses (i) the mechanism of action, pharmacokinetics, and pharmacodynamics of this novel drug, (ii) the efficacy, safety, and tolerability of LCZ696 in treatment of hypertension from the available trials, (iii) evidence from other contemporary trials on combined Neprilysin inhibitors, (iv) future trials and areas of research to identify hypertensive patient populations that would most benefit from LCZ696.

Keywords LCZ696 • Angiotensin receptor-neprilysin inhibitor • Hypertension

Introduction

In recent years, cell-signalling pathways and pathophysiological mechanisms have provided pharmacological targets for the development of novel antihypertensive drugs. Neprilysin is a neutral endopeptidase and its inhibition increases bioavailability of natriuretic peptides (NPs), bradykinin, and substance P, resulting in natriuretic, vasodilatatory, and anti-proliferative effects. In concert, these effects are prone to produce a powerful ventricular unloading and antihypertensive response. Isolated neprilysin inhibitors showed only a modest effect and hence went out of favour as stand-alone blood-pressure (BP) lowering agents.[1,2] Subsequently, drugs involving combined inhibition of neprilysin with renin–angiotensin–aldosterone system (RAAS) or endothelin-converting enzyme were developed and studied. Omapatrilat was the first-in-class representative drug of dual inhibition of neprilysin and the angiotensin-converting enzyme (ACE). Omapatrilat showed superior antihypertensive efficacy compared with other drug classes; however, the increased frequency and severity of angioedema observed with this drug lead to its withdrawal.[3,4] The increased frequency of angioedema was attributed to accumulation of bradykinin due to inhibition of ACE, neprilysin, and aminopeptidase.[5] These findings prompted the development of agents that combined neprilysin inhibitors with other molecules such as angiotensin-receptor blockers and endothelin-converting enzyme inhibitors. Valsartan/sacubitril (LCZ696, Novartis Pharmaceuticals) is a first-in-class angiotensin II-receptor neprilysin inhibitor (ARNI). Valsartan/sacubitril is a novel drug not only for the treatment of heart failure but it is also likely to be a useful antihypertensive drug. The aim of this concise review is to present the available data of ARNIs and discuss its role in management of hypertension.

Mechanism of action

Natriuretic peptides are a group of hormones that have potent effects on sodium and fluid balance. Additionally, they act to inhibit RAAS, reduce sympathetic drive, and have both antihypertensive and anti-proliferative effects.[6,7] Three types of NPs have been

* Corresponding author. Tel: +1 212 523 7373, Fax: +1 212 523 7765, Email: messerli.f@gmail.com

identified: Atrial NP (ANP) and Brain or B-type NP (BNP), released from the atria and left ventricle, respectively, in response to increased filling pressures and increased cardiac chamber wall stress, act to promote natriuresis, diuresis, and vasodilation.[8] The third, C-type NP (CNP) is found in the central nervous system, kidneys, and vascular endothelial cells; however, the significance of this peptide on the cardiovascular system has not been well established.[9,10] Neprilysin (also known as neutral endopeptidase 24.11) is a zinc-dependent metallopetidase that catalyses the degradation of various peptides including ANP, BNP, and bradykinin, as well as contributes to the breakdown of angiotensin II.[11] Thus inhibition of neprilysin in order to increase circulating levels of NPs has been studied for its therapeutic effect on BP. Though neprilysin inhibition alone has little, if any, antihypertensive effect, concomitant inhibition of both neprilysin and RAAS has demonstrated to synergistically lower BP.

Omapatrilat, an inhibitor of neprilysin and ACE is the most studied vasopeptidase inhibitor. In monotherapy, it has shown greater efficacy in lowering BP than ACE-inhibitors and calcium-channel blockers.[12,13] However, it was associated with an unacceptable risk of angioedema due to excessive inhibition of bradykinin degradation (presumably via neprilysin, ACE, and aminopeptidase P).[3–5] In contrast to omapatrilat, in LCZ696, the ACE inhibition has been replaced with an angiotensin II-receptor blocker (ARB) which has lesser effect on bradykinin[14] and thus a lower risk of angioedema.[15,16] Conceptually, this drug provides the vasodilatory and natriuretic properties of NPs concomitant with inhibitory effects on endothelin, vasopressin, sympathetic activity, and RAAS, but with an improved adverse effect profile[17] (*Figure 1*).

Pharmacokinetics and pharmacodynamics

LCZ696 is an oral tablet composed of a prodrug AHU377 (which is rapidly metabolized in to the active neprilysin inhibitor LBQ657 by enzymatic cleavage of its ethyl ester) and valsartan, a well-established ARB. These two molecular components are present in a 1:1 molar ratio. The maximal concentration of the valsartan component of LCZ696 is reached in 1.7–2.2 h, and 0.5–1.1 h for AHU377 with the active metabolite LBQ657 at peak concentration within 1.9–3.5 h. Mean $t_{1/2}$ values range from 1.1 to 3.6 h for AHU377, 9.9–11.1 h for LBQ657, and 8.9–16.6 h for valsartan.[18] LBQ657 exerts its inhibitory effect on neprilysin leading to an observed increase in both atrial natruretic peptide and guanosine monophosphate (cGMP).[18,19] A dose escalation study in 83 healthy participants showed a maximal 40% increase mean cGMP levels at 4 h and significant increases at 12 h post-dose with return to baseline levels at 24 h after administration of LCZ696.[18] In the same study, significant dose-dependent effects of the valsartan moiety lead to increases in renin concentration (93–634%), plasma renin activity (280–1768%), and angiotensin II (241–1188%) compared with placebo. A significant increase of RAAS biomarkers were still observed 24 h after dosing.

These results demonstrated a potent dual neurohormonal effect of LCZ696 on neprilysin and the angiotensin receptor. Peak concentrations of LBQ657 and valsartan were reached within a similar time frame demonstrating comparable pharmacokinetic properties. The pharmacodynamics of these two agents is also similar, exemplified by the maximal concentrations of cGMP and RAAS biomarkers

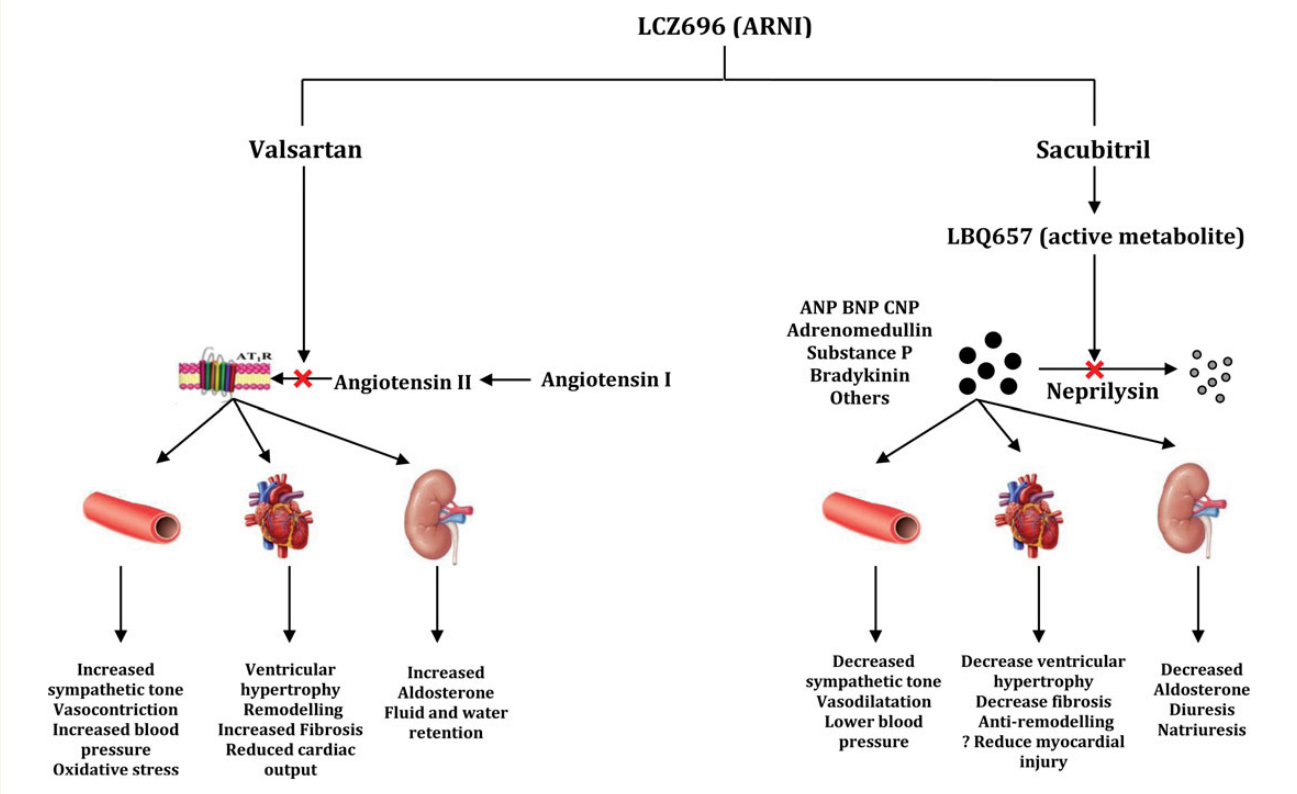

Figure 1 Schematic diagram showing mechanism of action of LCZ696.

being reached in parallel at 4 h. This is in contrast with omapatrilat which exerted delayed neprilysin inhibition when compared with ACE inhibition.[20,21] Though the clinical significance of this distinction is not currently known, LCZ696 may have a more balanced participation of its two mechanisms of action in controlling BP which may potentiate its overall efficacy. Moreover, the sustained pharmacodynamic effect of both the valsartan and LBQ657 moieties allows for once-daily dosing of LCZ696 for treatment of hypertension.

Clinical trials of angiotensin II-receptor neprilysin inhibitor in hypertension

Relevant articles were identified by searching MEDLINE using the following keywords and Medical Subject Headings (MeSH) terms: neprilysin inhibitor, LCZ696, angiotensin-receptor neprilysin inhibitor, hypertension, and/or heart failure. We screened the title and abstract of possibly relevant citations and retrieved all randomized control trials published until 2015, that studied or reported the effects of neprilysin inhibitors on BP.

Ruilope *et al.*[22] reported the first proof-of-concept trial with LCZ696 that investigated the antihypertensive effects of LCZ696 when compared with the angiotensin-receptor blocker—valsartan. In the multi-centre, randomized, double-blinded, placebo-controlled, active-comparator study involving 1328 patients of 18–75 years of age with mild-to-moderate essential hypertension were randomly assigned to 8 weeks of double-blind treatment in one of eight groups of daily dose: 100, 200, and 400 mg LCZ696; 80, 160, and 320 mg valsartan; 200 mg AHU377; or placebo. The primary outcome of the trial was the mean sitting diastolic BP difference between the three single-dose pairwise comparisons of LCZ696 and valsartan doses (100 mg LCZ696 vs. 80 mg valsartan, 200 mg LCZ696 vs. 160 mg valsartan, and 400 mg LCZ696 vs. 320 mg valsartan).

The mean age of the trial population was 53 ($\pm$10.2) years, with 57% male and about 86% of patients younger than 65 years. The average duration of hypertension was 6.8 ($\pm$7.2) years. LCZ696 provided significantly superior reductions from baseline in mean sitting diastolic and systolic BP than valsartan at 8 weeks. When compared with 160 mg valsartan, 200 mg LCZ696 showed a higher reduction in mean sitting systolic BP ($-$11 vs. $-$5.69 mmHg, $P = 0.0006$) and mean sitting diastolic BP ($-$6.14 vs. $-$3.17 mmHg, $P = 0.0023$). Similarly, compared with 320 mg valsartan, 400 mg LCZ696 showed a significantly higher reduction in mean sitting systolic BP ($-$12.5 vs. $-$6.44 mmHg, $P < 0.0001$) and mean sitting diastolic BP ($-$6.85 vs. $-$4.15 mmHg, $P = 0.0055$). The reduction in mean sitting diastolic and systolic BP for 100 mg LCZ696 vs. 80 mg valsartan did not reach statistical significance. In a subgroup of 427 patients who underwent ambulatory BP monitoring, significant differences in 24-h mean ambulatory systolic BP were recorded for 200 mg LCZ696 vs. 160 mg valsartan ($-$3.23 mmHg) and 400 mg LCZ696 vs. 320 mg valsartan ($-$5.14 mmHg) for the 8-week treatment period ($P < 0.05$). However, differences in 24-h mean ambulatory diastolic BP between LCZ696 and corresponding valsartan doses were small and not significant.

Recently, Kario *et al.*[23] published results of second hypertension trial of LCZ696 which was a multi-centre, randomized, double-blinded, placebo-controlled of 389 Asian patients aged $\geq$18 years with mild-to-moderate essential hypertension. After a 4-week run-in period, patients were randomized to 100, 200, or 400 mg LCZ696 or placebo for an 8-week double-blind period. The primary endpoint was mean difference across the three single-dose pairwise comparisons of LCZ696 vs. placebo (100, 200, and 400 mg LCZ696 vs. placebo) in clinic diastolic BP after the 8-week treatment period. When compared with placebo, the mean differences in change from baseline in clinic diastolic BP was $-$7.84, $-$7.29, and $-$8.76 mmHg for LCZ696 100, 200, and 400 mg, respectively. Likewise, compared with placebo, the mean differences in change from baseline in clinic systolic BP were $-$11.86, $-$12.57, and $-$15.38 mmHg for LCZ696 100, 200, and 400 mg, respectively. All doses of LCZ696 were associated with significant reductions in 24-h, daytime, and nighttime ambulatory systolic, diastolic, and pulse pressures ($P < 0.0001$).

Compared with Caucasian patients, BP reduction by LCZ696 tended to be greater in Asian patients with hypertension indicating that this drug may be particularly suitable in this population.[23] Asian hypertensive patients are characterized by higher salt sensitivity and higher salt intake, resulting in suppression of renin–angiotensin system.[24,25] These characteristics may result in higher prevalence of stroke, which is more directly associated with systolic BP. Thus, the increase in NPs by neprilysin inhibition in combination with ARB exerts an incremental effect on BP compared with ARB-monotherapy in Asian hypertensive patients (e.g. salt sensitive or elderly). In addition, LCZ696 may also be an effective drug in resistant hypertensive patients.[26] Of note, compared with the same dose of valsartan, LCZ696 decreased systolic BP more than diastolic BP, resulting in a reduction of pulse pressure[22] (*Figure 2*). Although the precise mechanism remains to be elucidated, the direct effect of NPs and ARB on the vascular properties and/or reduced circulating volume may play a part in the preferential effect of LCZ696 on systolic BP.

Effects of angiotensin II-receptor and neprilysin inhibitor on blood pressure in patients with heart failure

The effect of LCZ696 on BP was evaluated in patients with HF with preserved ejection fraction (HFpEF) in the *Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion* (PARAMOUNT) trial.[27] This was a Phase II, randomized, parallel-group, double-blind, multicentre trial in patients with HFpEF. Participants were randomly assigned to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily. The trial reported BP changes in both arms at 12 and 36 weeks as one of the secondary outcomes. The trial involved 301 patients with HFpEF of which about 93% had hypertension. After 12 weeks of treatment, BP was reduced by $-$9.3 mmHg systolic and $-$4.9 mmHg diastolic in the LCZ696 group. In the valsartan group, the systolic BP was reduced by $-$2.9 mmHg while the diastolic BP was reduced by $-$2.1 mmHg ($P = 0.001$ for systolic and $P = 0.09$ for diastolic BP differences). The significant higher reduction in BP by LCZ696 when compared with valsartan persisted at 36 weeks.

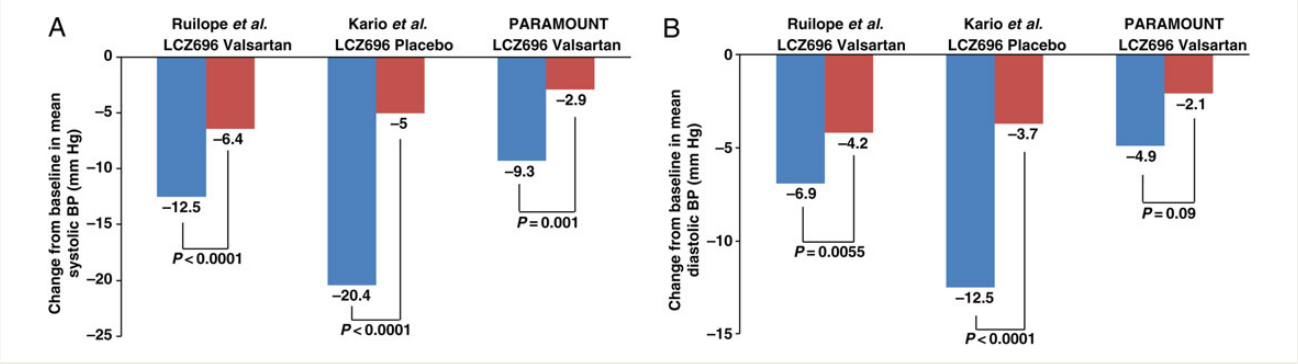

Figure 2 Change in mean (*A*) systolic and (*B*) diastolic blood pressure from baseline in three randomized controlled trials. Ruilope *et al.*[22] compared LCZ696 400 mg vs. valsartan 320 mg over 8 weeks. The PARAMOUNT trial compared LCZ696 200 mg twice daily vs. valsartan 160 mg twice daily over 12 weeks. Kario *et al.*[23] compared LCZ696 400 mg vs. placebo over 8 weeks.

While all the previous trials provided insights into the short term antihypertensive efficacy of LCZ696, the recently published *Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial* (PARADIGM-HF)[28] provided some data on the long-term effects of LCZ696 in patients with chronic heart failure and a reduced ejection fraction (HFrEF). The trial involved 8442 HFrEF patients with 71% patients having history of hypertension. LCZ696 (200 mg twice daily) was superior to Enalapril (10 mg twice daily) in reducing the risks of death and heart failure hospitalization. In the Supplementary material published with the study results, LCZ696 showed a significant reduction in systolic BP when compared with Enalapril [mean difference −2.7 (−3.07 to −2.34 mmHg, $P < 0.001$)] over a period of 3 years. It is unclear whether the favourable effects of LCZ696 on death and heart failure hospitalization is mediated primarily by reduction in BP or is independent of changes in BP.

Safety and tolerability of angiotensin II-receptor and neprilysin inhibitor in hypertension trials

LCZ696 showed relatively good safety profile. In the study by Ruilope *et al.*[22] during the 8-week treatment period, the most common adverse event was pruritus (2%) for LCZ696 200 mg and diarrhoea (3%) for LCZ696 400 mg. The rates were non-significant when compared with Valsartan. No cases of angioedema or deaths were reported. Discontinuation due to adverse events was 2% for LCZ696 200 mg, 1% each for LCZ696 400 mg, Valsartan 80 and 160 mg while 0 for Valsartan 400 mg. In the trial by Kario *et al.*,[23] the most common adverse event was nasopharyngitis and upper respiratory tract information. Incidence of dizziness was low (2.8%) and was not dose related. These side-effects was numerically higher in placebo groups when compared with LCZ696 100, 200, or 400 mg. Discontinuation due to adverse side-effects was 2% for LCZ696 200 mg, 1% for LCZ696 400, and 4.3% for placebo. Overall, all doses of LCZ696 were well tolerated, and no cases of angioedema or death were reported in either of these trials. Of note, patients with a history of angioedema were excluded in both the trials.

LCZ696 showed no significant change in heart rate from baseline in any of the trials.[22,23,27,28] Ruilope *et al.*[22] assessed orthostatic BP changes with LCZ696 and reported an incidence of 4–7%, with the lowest value in the 400 mg LCZ696 group. Future trials should study the occurrence of orthostatic hypotension at various dosages of LCZ696, since it is an important consideration in elderly patients. In addition, the effect of dietary salt intake on the response to this drug has not been previously studied and warrants future investigation.

Angiotensin II-receptor and neprilysin inhibitor in hypertension and specific comorbidities

Both diabetes and chronic kidney disease are associated with high prevalence of hypertension. The efficacy of ARNI in this important patient groups remains to be evaluated since in both the hypertension trials, patients with Type 1 and 2 diabetes and renal disease were excluded.[22,23] Kario *et al.*[23] found a negligible change in serum creatinine in placebo and LCZ696 groups. The mean change in serum creatinine from baseline was 0.02 mg/dL in the placebo group and 0.01 and 0.03 mg/dL in LCZ696 200 and 400 mg, respectively. In the PARAMOUNT trial involving patients with HFpEF, treatment with LCZ696 for 36 weeks resulted in lower serum creatinine and higher estimated glomerular filtration rate (eGFR) compared with valsartan.[29] The mean serum creatinine increase was 0.03 mg/dL in LCZ696 group and 0.09 mg/dL in the valsartan group ($P = 0.007$). Accordingly, the decline in eGFR was lower in the LCZ696 group than in the valsartan group (−1.5 vs. −5.2 mL/min per 1.73 m^2; $P = 0.002$). Moreover, in a recent meta-analysis, both omapatrilat and LCZ696 demonstrated a favourable effect on renal function compared with ACE-inhibitors or ARB monotherapy in patients with heart failure.[30] It remains to be seen whether similar nephro-protective effect of LCZ696 can be found in patients with hypertension.

Table 1 On-going clinical trials of LCZ696 in hypertension[a]

Trial number	Patient population	Brief title	Comparator
NCT01785472	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients With Essential Hypertension	Olmesartan
NCT01599104	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension	Olmesartan
NCT01870739	Essential hypertension	A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects With Hypertension	Olmesartan
NCT01615198	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients With Essential Hypertension	Olmesartan
NCT01681576	Salt-sensitive hypertension	Assessment of LCZ696 and Valsartan in Asian Patients With Salt-sensitive Hypertension	Valsartan
NCT01256411	Essential hypertension	A Long-term (12 Months) Safety, Tolerability and Efficacy Study of LCZ696 in Patients With Essential Hypertension	NA
NCT01601470	Mild-to-moderate hypertension	Evaluation of Drug-drug Interaction Between LCZ696 and Sildenafil in Subjects With Mild to Moderate Hypertension	Sildenafil
NCT01353508	Hypertension; heart failure and healthy volunteers	Sodium Excretion of LCZ696 in Patients With Hypertension; Heart Failure and Healthy Volunteers	Valsartan
NCT01692301	Hypertension	Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients With Hypertension	Olmesartan, Amlodipine, Hydrochlorthiazide
NCT01663233	Essential hypertension	Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Comparison With Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine	Amlodipine
NCT01646671	Severe hypertension	Safety and Tolerability and Efficacy of LCZ696 in Japanese Severe Hypertensive Patients	NA
NCT01631864	Hypertension, concurrent obesity	Evaluation of the Metabolic Effects of LCZ696 and Amlodipine in Obese Hypertensive Subjects	Amlodipine
ISRCTN11958993	Chronic kidney disease	Randomized multicentre pilot study of LCZ696 vs. Irbesartan in patients with chronic kidney disease: UK Heart And Renal Protection (HARP)-III	Irbesartan

[a]From ClinicalTrials.gov and International Standard Randomized Controlled Trials Number (ISRCTN) Register, NA, not applicable.

Neprilysin inhibition and Alzheimer's disease

Vodovar *et al.*[31] recently warned that the chronic use of neprilysin inhibitors may compromise β-amyloid peptide degradation in the brain, thereby possibly accelerate progression of Alzheimer's disease and cerebral amyloid angiopathy in patients at risk. In pre-clinical studies, mostly involving animal models, neprilysin inhibition has been associated with development of Alzheimer's dementia-like disease.[32,33] These observations need to be thoroughly tested in clinical trials. If confirmed in human subjects, this would be of much greater concern in hypertensive patients who are treated for years and even decades than in heart failure where survival is curtailed. Conceivably, the potential adverse effects of sacubitril on β-amyloid peptide degradation might be counterbalanced by ARB's beneficial vascular effects.[34] Regardless, this clearly indicates that the safety associated with the chronic use of neprilysin inhibitors, including LCZ696, needs to be scrutinized especially in patients at-risk such as those with mild cognitive impairment.

Other combined neprilysin inhibitor

Daglutril (Solvay Pharmaceuticals) is the first-in-class dual neprilysin–endothelin-converting enzyme inhibitor.[35] Endothelin-converting enzyme is implicated in conversion of Big-Endothelin1 into active endothelin-1 which binds to endothelin type-A receptors and causes vasoconstricton and increased anti-NPs.[36] Hence neprilysin and endothelin converting enzyme inhibition are likely to exert antihypertensive efficacy. However, till date, only one randomized control trial have been published evaluating the antihypertensive efficacy of daglutril involving patients with type 2 diabetes and nephropathy.[35] In a small randomized cross-over, double-blind placebo-controlled trial of 42 patients, when compared with placebo, 8 weeks of daglutril (300 mg/day) was associated with significant reduction of office systolic BP (-5.4 mmHg, $P = 0.028$) but not diastolic BP (-1.8 mmHg, $P = 0.245$). The drug was well tolerated and no serious treatment-related adverse events were reported in the trial.

Ongoing trials of angiotensin II-receptor and neprilysin inhibitor in hypertension

Currently, several trials are investigating the efficacy and safety of LCZ696 in treatment of hypertension. The *Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly* (PARAMETER) trial aims to compare the effect of LCZ696 vs. olmesartan on aortic

hemodynamics and ambulatory BP.[37] PARAMETER will include an estimated 432 patients with essential hypertension ≥60 years (mean sitting systolic BP 150–180 mmHg and pulse pressure >60 mmHg) who will be randomized either to once daily LCZ696 200 mg or olmesartan 40 mg. The primary endpoint is change in central aortic systolic pressure at 12 weeks measured non-invasively by waveform analysis using a brachial BP cuff linked to computer software. Other on-ongoing clinical trials, retrieved by searching ClinicalTrials.gov and International Standard Randomized Controlled Trials Number (ISRCTN) Registry, are listed in *Table 1*.

Perspective

Antihypertensive therapy with modern drugs, given as monotherapy or in combination, allows lowering of BP with comfort and convenience. Many drugs have an adverse effect profile close to or even better than placebo, are inexpensive, and allow once-daily dosing. Even resistant hypertension can most often be managed with combination therapy without causing inconvenient adverse effects. However, the antihypertensive efficacy of most commonly used drugs is remarkably similar; BP decreases to about the same extent whether therapy is initiated with a diuretic, a calcium-channel blocker, a beta-blocker, or an RAAS blocker. This would indicate that the risk/benefit ratio of many antihypertensive drugs is exceedingly low and some agents such as amlodipine have outstanding outcome data. Clearly, this represents a challenging milieu for introducing a new drug class. However, since safety is unlikely to be surpassed, a new arrival will have to document greater efficacy than other antihypertensive agents either in lowering the surrogate, i.e. BP, preferentially systolic and/or visit-to-visit BP variability and, even more importantly, in improving end-organ damage (vasculopathy, retinopathy, left-ventricular hypertrophy, and nephropathy) and outcomes (stroke, coronary artery disease, heart failure, and death). The outcomes data so far accumulated in heart failure seem to indicate that this may be indeed the case with Valsartan/sacubitril (LCZ696).

Conclusions

From the available evidence, LCZ696 have shown impressive reduction in systolic and diastolic BP; however, the long-term antihypertensive efficacy of LCZ696 has not been fully evaluated. Also the effect of LCZ696 on cardiovascular outcomes in patients with hypertension is unknown. In the PARADIGM trial, LCZ696 showed a striking reduction in cardiovascular mortality and morbidity in patients with HFrEF. However, it is to be seen whether LCZ696 confers similar long-term prognostic benefits in patients with hypertension. Further studies need to be conducted to elucidate the role of LCZ696 in patients with (i) diabetes, (ii) chronic kidney disease, (iii) elderly, (iv) resistant hypertension. Since blacks were underrepresented in the two published hypertension trials, future trials should include adequate black population. Most importantly, studies needs to be conducted comparing antihypertensive efficacy and outcome of LCZ696 with other drug classes such as calcium-channel blockers and diuretics.

Conflict of interest: F.H.M. is a consultant or advisory relationships with the following companies: Daiichi-Sankyo, Pfizer, Abbott, Servier, Medtronic, WebMD; L.M.R. served as advisor/speaker for Novartis; K.K. received research grant from Novartis, Teijin, and Takeda, consultant fee from Novartis, and received speakers bureau from Takeda, Mochida, and Daiichi Sankyo.

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